Journal of Surgical Oncology 62:284–287 (1996)

Early Carcinoma of the Gallbladder: An Elusive Disease

VINAY K. KAPOOR, MS, FACS, REBALA PRADEEP, MS, MCh, SANJIV P. HARIBHAKTI, MS, DNB, SADIQ S. SIKORA, MS, AND SATYENDRA P. KAUSHIK, PhD, FRCS
From the Department of Surgical Gastroenterology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India

Prognosis of carcinoma of the gallbladder can be improved by diagnosing the disease in the early stages. Records of 14 patients with early (UICC AJCC TNM stages I and II) carcinoma of the gallbladder were analyzed. Clinical presentation in all these patients was like benign biliary disease. Ultrasonography could diagnose carcinoma of the gallbladder in only five patients; in the remaining nine patients, even the ultrasonographic diagnosis was benign biliary disease. All patients were operated; carcinoma of the gallbladder was diagnosed at operation in two more patients, but it was first detected only after histological examination in seven patients. All patients except four had associated gallstones. Preoperative diagnosis of early carcinoma of the gallbladder is difficult. The only way to diagnose early carcinoma of the gallbladder is by early surgical treatment of patients with clinical features of benign biliary disease.

KEY WORDS: **cholecystectomy, cholecystitis, cholelithiasis, gallbladder neoplasms**

INTRODUCTION

Carcinoma of the gallbladder (CaGB) is common in such countries as Chile [1], Bolivia [2], Japan [3], and India [4]. It is the most common biliary tract malignancy and the fifth, fourth, and third most common gastrointestinal tract malignancy in the United States [5], United Kingdom [6], and India [4], respectively. CaGB is a lethal disease with poor prognosis; overall 1-year and 5-year survivals have been reported to be $<10\%$ and $<5\%$, respectively [5]. Median survival after diagnosis is only 6 months [7,8]. Prognosis is related to the tumor stage, most long-term survivors being patients with early stage disease only [9]. Prognosis in CaGB can therefore be improved by diagnosing patients in the early stages [10]. We report our experiences with early CaGB to highlight its elusive clinical presentation.

MATERIALS AND METHODS

The Sanjay Gandhi Post-Graduate Institute of Medical Sciences is a tertiary level referral hospital in northern India. Details of all patients with CaGB have been recorded prospectively on a proforma since January 1989. TNM staging as recommended by the UICC and AJCC was followed. Staging was based on operative and histopathological findings, and early CaGB was defined as stage I (T1 N0 M0—tumor invading mucosa or muscle) and stage II disease (T2 N0 M0—tumor invading perimuscular connective tissue but no extension beyond serosa or into the liver).

A total of 297 patients with CaGB were seen from January 1989 to December 1994. Records of 14 patients with early CaGB (stage I n = 6 and stage II n = 8) were analyzed.

RESULTS

Clinical diagnosis in all these patients was benign biliary disease (BBD). Ultrasonography (US) picked up the correct diagnosis in only five patients; in the remaining nine patients, the US diagnosis was BBD. Cholecystec-

Accepted for publication March 6, 1996.

Address reprint requests to V.K. Kapoor, Department of Surgical Gastroenterology, SGPGIMS, Lucknow, 226 014 India.

Part of this material was presented at the First Joint Meeting of the British Association of Surgical Oncology, European Society of Surgical Oncology, and Section of Oncology, German Surgical Society at Heidelberg, Germany (June 8–11, 1994) and was published as an abstract in the European Journal of Surgical Oncology 3:298, 1994.

TABLE I. Diagnosis of Carcinoma of the Gallbladder

	Stage I n = 6	Stage II n = 8	Total n = 14
Pre-operative (ultrasonography)	2	3	5
Per-operative	2	0	2
Postoperative (histology)	2	5	7

tomy was performed in all patients. CaGB was not suspected at operation and was first revealed after histological examination in seven patients (Table I). Gallstones were present in 10 (71%) patients.

Stage I (n = 6)

Mean age of the patients was 52 years (range 40–58 years) and all except one were female. Median duration of symptoms was 5 months (range 6 weeks to 3 years); all except one patient had symptoms for <1 year. The clinical diagnosis in all these patients was BBD (chronic cholecystitis 3, mucocele of the gallbladder 2, and choledocholithiasis 1). Serum alkaline phosphatase was elevated (179 and 195 IU/L) in two patients who did not have jaundice and had normal serum bilirubin. US showed gallbladder mass in two patients; gallstones were present in all other patients, one patient also had choledocholithiasis.

The patient with choledocholithiasis underwent endoscopic retrograde cholangiography and endoscopic papillotomy and stone extraction. All patients were operated. Five patients (including the two in whom US had showed a gallbladder mass) were found to have a gallbladder mass. Per-operative diagnosis was CaGB in four patients, but one was not suspected to have CaGB even at operation and the per-operative diagnosis in this patient was BBD. Simple cholecystectomy was performed in five patients and radical cholecystectomy (including wedge of liver and lymph nodes in the hepatoduodenal ligament) in one. Gallstones were present in four patients. Tumor was extending into the muscle layer (pT1b) in all patients. Lymph nodes in the patient in whom radical cholecystectomy was performed were negative on histological examination.

One patient developed obstructive jaundice due to enlarged lymph nodes 14 months after cholecystectomy. Intrahepatic segment III cholangio-jejunostomy was performed; she died 20 months after cholecystectomy. The remaining patients received postoperative radiotherapy. The patient in whom radical cholecystectomy was performed died at 8 months, and four patients in whom simple cholecystectomy was performed are alive with no evidence of disease at 15, 24, 25, and 31 months.

Stage II (n = 8)

Mean age of the patients was 56 years (range 28–78 years); 5 were female and 3 male. Median duration of symptoms was 6 months (range 2 weeks to 10 years); all except two patients had symptoms for <1 year. The clinical diagnosis in all these patients was BBD (chronic cholecystitis 4, mucocele of the gallbladder 2, and choledocholithiasis 2). Serum alkaline phosphatase was elevated (212 and 302 IU/L) in two patients who did not have jaundice and had normal serum bilirubin. US showed gallbladder mass in three patients, gallbladder polyp without gallstones in one patient, and cholelithiasis in four patients (with choledocholithiasis in 2). Computed tomography (CT) was performed in two patients in whom a mass was seen on US; both were shown to have a gallbladder mass on CT also and CT diagnosis was CaGB in both these patients. Fine-needle aspiration cytology was performed in three patients in whom US had revealed a gallbladder mass and was positive for malignant cells in all.

All patients were operated. Five patients (including the three in whom US had showed a gallbladder mass) were found to have gallbladder mass. Per-operative diagnosis was CaGB in three patients, but two were not suspected to have CaGB even at operation and the per-operative diagnosis in these two patients was BBD. Simple cholecystectomy was performed in seven patients and radical cholecystectomy (including wedge of liver, common bile duct, and lymph nodes in the hepatoduodenal ligament) in one. Common bile duct exploration was also performed in two patients with choledocholithiasis. Gallstones were present in six patients. Tumor had extended into the perimuscular connective tissue (pT2) in all patients. Lymph nodes in the patient in whom radical cholecystectomy was performed were negative on histological examination.

The patient in whom radical cholecystectomy was performed had bile leak and major wound infection and left the hospital against medical advice (presumed 30-day death). The remaining seven patients in whom simple cholecystectomy was performed received postoperative radiotherapy. Five patients died at 3, 3, 7, 9, and 24 months, and two are alive at 16 and 38 months.

DISCUSSION

Clinical presentation in all our patients with early (stages I and II) CaGB was like BBD. US detected CaGB in only one-third of these patients. As many as half were incidental carcinomas detected for the first time on histological examination after cholecystectomy for presumed BBD.

Symptoms and signs of early CaGB are nonspecific and indistinguishable from those of BBD. Clinical diagnosis in all our patients with early CaGB was BBD. Similar experience has been reported by Aretxabala et

al. [11] who observed that none of the 15 early CaGBs was diagnosed clinically.

Preoperative diagnosis of early CaGB remains difficult. Even in an area where CaGB is common, only 7 out of 143 patients with CaGB had early lesions localized to the gallbladder wall [12]. In areas where CaGB is not frequently seen, diagnosis is even more difficult. Silk et al. [7] reported 71 patients with CaGB, 62 of whom had advanced disease; none could be diagnosed preoperatively. US has been reported to detect early CaGB [13]. US findings in CaGB are thickening of the gallbladder wall, polypoid mass protruding into the gallbladder lumen, and a gallbladder mass involving adjacent organs [14]. US, although a sensitive investigation for clinically overt CaGB, fails to detect early disease [15]. Presence of gallstones further complicates US detection of early lesions, as a small mass or minimal thickening of the gallbladder wall may get overshadowed by the calculi [13]. Three of our patients who could be diagnosed as CaGB on US and one in whom US revealed a polyp did not have associated gallstones, thus making US evaluation of the gallbladder easier. In another series, US could diagnose CaGB in only 3 out of 54 resectable cases [1].

CT is useful in demonstrating CaGB and shows the same findings as seen on US [16]. Ouchi et al. [10] reported that combined use of imaging techniques like US, CT, drip infusion cholangiography, and angiography resulted in detection of early CaGB. Endoscopic ultrasonography is another promising imaging investigation to detect early lesions in CaGB. Chijiwa et al. [17] also reported that imaging techniques like US, CT, and endoscopic ultrasonography contribute to the detection of CaGB at an early stage. Yamaguchi et al. [18], however, reported 31 patients with T1 and T2 tumours in whom US, CT, drip infusion cholangiography, and endoscopic retrograde cholangiography could not detect CaGB. CT detected CaGB in two of our patients with stage II disease, but it was performed in these patients only when CaGB was suspected after US had revealed a gallbladder mass. However, since most patients with early CaGB present clinically as BBD and US also does not raise the suspicion of CaGB, investigations such as CT, endoscopic ultrasonography, drip infusion cholangiography, endoscopic retrograde cholangiography, and angiography are not indicated and would not be performed in them.

Once US or CT demonstrates a gallbladder mass, US guided fine-needle aspiration cytology is an accurate and safe method of establishing the diagnosis of CaGB. In a large series of 88 patients, Zargar et al. [19] reported an accuracy of 90%, sensitivity of 89%, and specificity of 100%; the predictive value of a positive result was 100%.

Elevated serum alkaline phosphatase in the absence of jaundice in patients with clinical features of BBD may arouse the suspicion of CaGB. This phenomenon was observed in four of our patients with early CaGB.

Detection and treatment of premalignant lesions such as polyps and adenomyomatosis in the gallbladder also result in diagnosis of early CaGB. One of our patients with early CaGB had a gallbladder polyp detected on US. Asymptomatic small (<10 mm diameter) polyps and adenomyomatosis with normal gallbladder wall need only follow up with ultrasonography. Cholecystectomy, however, should be performed in presence of symptomatic or large (>10 mm diameter) polyps and thickening and/or irregularity of the gallbladder wall in adenomyomatosis even if they are asymptomatic [20].

Xanthogranulomatous cholecystitis is a destructive chronic inflammatory lesion of the gallbladder that presents with symptoms of BBD. A mass may be present, however, on US, CT, and even at laparotomy, and it may be difficult to differentiate xanthogranulomatous cholecystitis from CaGB [21]. Xanthogranulomatous cholecystitis is very common in northern India. It was present in 50 (4%) out of ~1,300 cholecystectomies performed in our department in 6 years (unpub. data). Per-operative diagnosis in three of the patients reported here who were found to have a gallbladder mass at laparotomy was BBD (including xanthogranulomatous cholecystitis).

It is recommended that all gallbladders removed for presumed BBD should be opened and examined in the operation room before the abdomen is closed and any suspicious areas should be subjected to frozen section examination. Simple cholecystectomy alone is sufficient for Tis and T1a lesions, but radical cholecystectomy (cholecystectomy with wedge resection of the gallbladder bed in the liver and dissection of lymph nodes in the hepatoduodenal ligament) should be performed in T1b and T2 lesions [1,9]. Simple cholecysteomy was, however, performed in all our patients (except two in whom radical cholecystectomy was performed because they had enlarged pericholedochal lymph nodes and were thought to have stage III disease), because we have been prospectively evaluating the role of simple cholecystectomy followed by radiotherapy in early CaGB. All removed gallbladders should be subjected to careful and detailed histological examination with multiple serial sections to detect incidental (inapparent) carcinomas [3,18]. Half of our patients with early CaGB had incidental carcinomas; Aretxabala et al. also have reported that 11 out of 15 early CaGBs [11] and 30 out of 54 resectable CaGBs [1] could be diagnosed only after histological examination. All except one of the 14 early CaGBs reported by Gall et al. [22] were incidental carcinomas. In such situations when CaGB is diagnosed after histological examination, T1 lesions may be kept on follow up, but a second operation is recommended for T2 lesions when radical cholecystectomy should be performed [3,18]. We have been evaluating the role of postoperative radiotherapy, however, in such situations.

All patients with early carcinoma of the gallbladder

presented clinically as benign biliary disease and the majority could not be diagnosed even on ultrasonography. The only way to diagnose the majority of patients with early carcinoma of the gallbladder is, therefore, early surgical treatment of all patients with symptoms of benign biliary disease. Aretxabala et al. [11], in fact, go even further and suggest prophylactic cholecystectomy for all patients with gallstone disease in areas with a high incidence of carcinoma of the gallbladder because of the difficult pre-operative diagnosis of early lesions. We tend to agree with them, because this will result in detection of more incidental/inapparent carcinomas, which are usually in the early stages, are resectable for cure and have better prognosis.

REFERENCES

1. Aretxabala X de, Roa I, Burgos L, Araya JC, Fonseca L, Wistuba I, Flores P: Gallbladder cancer in Chile: A report on 54 potentially reectable tumours. Cancer 69:60–65, 1992.
2. Rios Dalenz J, Takabayashi A, Henson D, Strom BL, Soloway RD: The epidemiology of cancer of the extrahepatic biliary tract in Bolivia. Int J Epidemiol 12:156–160, 1983.
3. Shirai Y, Yoshida K, Tsukada K, Muto T: Inapparent carcinoma of the gallbladder. Ann Surg 215:326–331, 1992.
4. Shukla VK, Khandelwal C, Roy SK, Vaidya MP: Primary carcinoma of the gallbladder. J Surg Oncol 28:32–35, 1985.
5. Piehler JM, Crichlow RW: Primary carcinoma of the gallbladder. Surg Gynecol Obstet 147:929–942, 1978.
6. Carty NJ, Johnson CD: Carcinoma of the gallbladder: A survey of cases in Wessex 1982–1989. J R Coll Surg Edinb 36:238–241, 1991.
7. Silk YN, Douglass HO, Nava HR, Driscoll DL, Tartarian G: Carcinoma of the gallbladder. Ann Surg 210:751–757, 1989.
8. Donohue JH, Nagorney DM, Grant CS, Tsushima K, Ilstrup DM, Adson MA: Carcinoma of the gallbladder. Arch Surg 125:237–241, 1990.
9. Ouchi K, Suzuki M, Tominaga T, Saijo S, Matsura S: Survival after surgery for cancer of the gallbladder. Br J Surg 81:1655–1657, 1994.
10. Ouchi K, Suzuki M, Saijo S, Ito K, Matsuno S: Do recent advances in diagnosis and operative management improve the outcome of gallbladder carcinoma? Surgery 113:324–329, 1993.
11. Aretxabala X de, Roa I, Araya JC, Burgos L, Huenchullan I, Miyazaki I: Operative findings in patients with early forms of gallbladder cancer. Br J Surg 77:291–293, 1990.
12. Chattopadhyay TK, Kumar VK, Kapoor VK, et al.: Carcinoma of the gallbladder—can we do anything? Postgrad Med J 64:593–595, 1988.
13. Koga A, Yamauchi S, Izumi Y, Hamanaka N: Ultrasonographic detection of early and curable carcinoma of the gallbladder. Br J Surg 72:728–730, 1985.
14. Daly BD, Cheung H, Arnold M, Metreweli C: Ultrasound in the diagnosis of gallbladder carcinoma in Chinese patients. Clin Radiol 48:41–44, 1993.
15. Pal A, Sharma SK, Pal A, et al.: Ultrasonogrpahic evaluation of carcinoma of the gallbladder. Natl Med J India 3:167–170, 1990.
16. Weiner SN, Koenigsberg M, Morehouse H, Hoffman J: Sonography and computed tomography in the diagnosis of carcinoma of the gallbladder. Am J Roentgenol 142:735–739, 1984.
17. Chijiwa K, Sumiyoshi K, Nakayama F: Impact of recent advances in hepatobiliary imaging techniques on the preoperative diagnosis of carcinoma of the gallbladder. World J Surg 15:322–327, 1991.
18. Yamaguchi K, Tsuneyoshi M: Subclinical gallbladder carcinoma. Am J Surg 163:382–386, 1992.
19. Zargar SA, Khuroo MS, Mahajan R, Jan GM, Shah P: US-guided fine-needle aspiration biopsy of gallbladder masses. Radiology 179:275–278, 1991.
20. Aldridge MC, Bismuth H: Gallbladder cancer: The polyp-cancer sequence. Br J Surg 77:363–364, 1990.
21. Houston JP, Collins MC, Cameron I, Reed MWR, Parsons MA, Roberts KM: Xanthogranulomatous cholecystitis. Br J Surg 81:1030–1032, 1994.
22. Gall FP, Kockerling F, Scheele J, Schneider C, Hohenberger W: Radical operations for carcinoma of the gallbladder: Present status in Germany. World J Surg 15:328–336, 1991.

COMMENTARY

The results reported are comparable to other series where poor long-term survival is reported in spite of the findings of early cancer. I would take issue with the performance of needle biopsy (percutaneous) preoperatively since it will not obviate the need for cholecystectomy and may contaminate the operative field. Opening the specimen prior to termination of the procedure should be routine.

Bernard Gardner, MD
University of New Jersey
Medical and Dental School
Newark, New Jersey 07103-2757